SUMMARY BASIS OF APPROVAL

Reference No.: 96-0350

Licensed Name: Alteplase

Applicant: Genentech, Inc.
460 Point San Bruno Blvd.
South San Francisco, CA 94080

Trade Name: Activase®

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I. INDICATION

This Summary Basis for Approval is for a new indication for Activase®, Alteplase in the management of acute ischemic stroke. Activase is currently indicated in the management of acute myocardial infarction and acute massive pulmonary embolism.

The additional indication statement for acute ischemic stroke is as follows:

> Activase is indicated for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability.
>
> Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method similarly sensitive for the presence of hemorrhage (see Contraindications).

II. DOSAGE FORMS, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. *Dosage Forms and Route of Administration*

Activase is for intravenous (IV) administration only, and is supplied as a sterile, lyophilized powder for reconstitution with sterile water for injection (USP). Upon reconstitution, the resulting solution is 1 mg/mL. Activase is commercially available in 100 mg or 50 mg vial sizes.

B. *Recommended Dosage*

Acute Ischemic Stroke

The recommended dose is 0.9 mg/kg (maximum of 90 mg) infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus over 1 minute.

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin during the first 24 hours after symptom onset has not been investigated.

THE DOSE FOR TREATMENT OF ACUTE ISCHEMIC STROKE SHOULD NOT EXCEED 90 mg.

III. MANUFACTURING AND CONTROLS

No new significant manufacturing and control information was provided as part of this application.

A. *Environmental Impact Assessment Report*

An Environmental Assessment Report was submitted by Genentech on March 29, 1996 as a supplement to the PLA. A review of this report indicated that no significant adverse environmental effects were expected to result from additional product produced for this supplemental clinical indication. A finding of no significant impact on the environment was prepared.

IV. PHARMACOLOGY/TOXICOLOGY

No new Pharmacology/Toxicology information was provided as part of this application that was pertinent to approval.

V. MEDICAL

A. *Background*

Ischemic stroke is the most common neurological disorder causing death and disability among adults, with an incidence in the U.S. of approximately 500,00 per year. It is the third-ranked cause of death in adults in the U.S. (following heart disease and cancer).

This application is the first product given marketing approval for an indication for treatment of acute stroke. Treatment of acute stroke has previously focused upon medical and supportive care. These include adequate pulmonary care and maintenance of respiratory function, prevention of aspiration, cardiovascular monitoring and management, and fluid, electrolyte, and metabolic monitoring and management.

The rationale for the use of thrombolytic agents in acute thrombotic stroke is readily apparent. The results of many studies of thrombolytics in patients with stroke are reported in the medical literature. Some reports have been encouraging with respect to demonstrating improvement in outcome, but the reports also highlight the risk of intracranial hemorrhage associated with this class of agents.

Activase is recombinant human tissue-type plasminogen activator (t-PA). It is produced by expression of the human gene for tPA in CHO cells. Activase is glycosylated, with 527 amino acids. The mechanism of action is believed to be the enzymatic cleaving of plasminogen into plasmin, which will then increase fibrinolysis. Activase exhibits fibrin specificity. It is considerably more active when bound to the surface of fibrin, thus promoting release of plasmin in the direct vicinity of fibrin. Activase is distributed largely to the vascular space and is rapidly cleared from the plasma; the half life is a few minutes.

Activase previously carried indications for acute myocardial infarction (AMI) and massive pulmonary embolism. There are two recommended dosage regimens for AMI. The older regimen (termed 3-hour infusion) is 100mg total, given 6-10% as a bolus, 50-54% as infusion in the first hour, then 20% over each of the two succeeding hours. For patients weighing less than 65kg, the dose is 1.25 mg/kg, distributed in the same proportions. The second, newer AMI regimen is termed the accelerated infusion. It is, for patients weighing more than 67kg, a total of 100 mg, given as a 15 mg IV bolus, followed 50mg in a 1/2 hour infusion, followed by 35 mg over the next hour. Total infusion duration is 90 minutes. For patients weighing less than 67kg, the dose is 15mg bolus, 0.75mg/kg in a 1/2 hour infusion, followed by 0.5mg/kg in a 1 hour infusion.

The pulmonary embolus regimen is 100mg administered by infusion over 2 hours.

B. *Overview of Clinical Studies*

Primary support for the use of Activase for the management of acute ischemic stroke was based on the results of "The National Institute of Neurological Disorders and Stroke (NINDS) t-PA Stroke Trial" (Genentech Protocol A0228s). This study consisted of two sequentially conducted studies. The primary endpoint of the Part 1 Study was early neurological improvement within 24 hours of stroke onset. Part 1 Study results generated the hypothesis of clinical benefit assessed by 3 month outcomes, which was tested in the Part 2 Study. Part 2 was designed as a pivotal Phase 3 trial to address safety and efficacy at 3 months.

Prior to Study A0228s initiation, a small pilot, study 87-906, "Protocol for the Evaluation of Tissue Plasminogen Activator Early in the Course of Acute Stroke," was conducted to evaluate safety and neurological activity of Activase in patients with acute ischemic stroke. This was a dose-ranging study followed by feasibility testing of a placebo-controlled trial. Information obtained from this study was used to support the design of Study A0228s.

In addition to the Activase clinical investigations described, the "European Cooperative Acute Stroke Study (ECASS)" was an evaluation of Actilyse® Alteplase, for the management of acute ischemic stroke. This study was different in design and treatment regimen compared to the NINDS Stroke Trial. This study did not demonstrate a favorable risk-benefit assessment. The safety aspects of this study are relevant to consideration of the current PLA supplement.

C. *The NINDS tPA Stroke Trial: Design*

1. Overview

This protocol, formally entitled "The NINDS tPA Stroke Trial" consisted of two separate studies that were conducted consecutively with identical procedures at the same set of study sites. They are distinguished by the different primary endpoints and the prospective designation that patients enrolled on November 3, 1992 and thereafter were considered part of the second study. These two studies will be called the Part 1 study and the Part 2 study in this document for consistency with the publication resulting from the studies (NEJM 1995; 333:1581-7).

The Part 1 study was designed as a study of the early activity effects of tPA in stroke, without plans for an immediate continuation into an additional study. By late in the conduct of this study the investigator group determined that the outcome at 90 days was more informative of clinical benefit, and for a variety of reasons wished to proceed directly into a phase 3 efficacy study. Thus it was decided to add a second study, of approximately 300 patients, which would commence immediately upon ending the enrollment into the Part 1 study. CBER was involved in the discussions that arrived at this plan. Interim analyses of the Part 1 study efficacy and safety results were used in the selection of the primary endpoint for the Part 2 study.

While all procedures were the same for the Part 1 study and the Part 2 study, the analytic plans and endpoints were not identical. The review of the study design applies to both Part 1 and Part 2 studies, except as noted. The analytic plan of the protocol was determined by the investigator group. There were additional discussions between Genentech (the manufacturer), and CBER

regarding an analytic plan for Genentech to use to support an application for licensure. These analysis plans evolved with time and further discussions, and are briefly detailed further below.

The Part 2 study constituted the prospective hypothesis testing study. The Part 1 study was the exploratory study for hypothesis generation, and had a supportive role in evaluation of efficacy. For purposes of safety assessments the studies were combined to increase power for discernment of risks associated with the therapy.

2. Design

These were two consecutive, analytically separate, double-blind, randomized, placebo-controlled studies. The studies were conducted at 39 treatment sites. Each group of treatment sites was administered by 1 of 9 local Clinical Centers. The single central Coordinating Center was at Henry Ford Hospital (HFH).

Patients with acute ischemic stroke were randomized to one of 2 treatment arms, IV tPA or IV placebo. Treatment had to be initiated within 180 minutes of stroke onset. Patient randomization was stratified by the time from stroke onset to initiation of treatment into two cohorts, those treated within 90 minutes of onset (0-90min) and those treated after (91-180min). The protocol required that each regional group of treatment sites maintain accrued number of patients in a close to balanced manner in the two time strata. Because of the constraints of evaluating patients and initiating treatment within the proscribed time limits, randomization was decentralized to eliminate a potential delay with centralized randomization. Patients were not to receive any study treatment until after all screening evaluations were completed, and patients were not deemed enrolled and randomized until they began to receive the study treatment.

Blinding was incorporated into the studies by using blind labeled vials and identical administration regimens for the two arms. The outcome assessments of 1day, 1 week and 3 months were to be performed by personnel not present during the study treatment infusion.

Study treatment consisted of either tPA or placebo, given IV, with time from stroke onset to start of the study treatment determining the time stratum of the patient. Patients were deemed to be enrolled and randomized only at the moment the study treatment began. The dosage of tPA was 0.9 mg/kg up to maximum of 100kg of body weight, and 90 mg for all patients of weight > 90 kg. The treatment was given as 10% of the material as a 1-2 minute bolus, followed by the remainder as an infusion to be completed at 60min after the start of the bolus. Placebo was prepared in equal volumes and given identically.

Anticoagulant and anti-platelet agents were prohibited during the first 24 hours. After that time, use of these agents was at the discretion of the investigators after confirming absence of hemorrhage on the 24 hr CT scan, and was recorded in the concomitant medication list.

3. Patient eligibility criteria

Inclusion Criteria

1) Age 18 or older
2) Clinical diagnosis of acute ischemic stroke with measurable neurologic deficit
3) Time of onset is <180 min of when treatment can begin,
4) The Clinical Center administering the specific treatment site has adequate balance of patients between strata (enrollment into 90-180 min stratum was permitted only if the number of patients in 90-180 min. stratum is not more than 2 greater than in the 0-90 stratum).

Exclusion Criteria

1) Only minor stroke or symptoms rapidly improving at time of infusion start
2) Evidence of hemorrhage on CT scan
   No other formal CT scan exclusion criteria.
3) Clinical presentation suggesting subarachnoid hemorrhage
4) Female & lactating or pregnant
5) Platelet count < 100,000, PT > 15, Heparin within 48 hrs & PTT > normal, or
   Patient on oral anticoagulants.
6) Major surgery or body trauma within 14 d prior; serious head trauma within 3 mo
7) Hx of GI or UT hemorrhage in prior 21 d.
8) Noncompressible arterial puncture within 7d; LP within 7 d
9) Systolic BP > 185 or diastolic > 110
10) Hx of stroke in prior 3 mo, prior ICH suggesting risk factor.
11) Serious medical illness that would interfere with trial
12) Glucose <50 or > 400
13) Clinical presentation consistent with MI or postMI pericarditis
14) Seizure at onset of stroke

There were no formal CT scan-based exclusion criteria other than the finding of hemorrhage. However, there were practices that may have resulted in *de facto* exclusion criteria. When investigators observed what was subjectively felt to be significant early infarct signs on the screening CT scan, they would frequently re-question the patient and/or family regarding the time of onset of symptoms. In the course of re-questioning they would often determine that the stroke onset was earlier than previously reported, and the patient would be excluded on the basis of too long an elapsed time from onset. Thus, in practice, there were some exclusions from the study resulting from observation of infarct-related CT scan findings.

4. Evaluations and Endpoints

The primary clinical outcome evaluations consisted of 4 outcome scales: the Barthel Index (Barthel), the Modified Rankin Scale (Rankin), the Glasgow Outcome Scale (Glasgow) and the NIH Stroke Scale (NIH-SS).

Baseline evaluations included the NIH Stroke Scale (NIH-SS) and cranial CT scan. Close clinical monitoring was conducted during the first 24 hours after study treatment, and NIH-SS and CT scans were repeated at 24 hrs and at 1 week (with Barthel Index and Modified Rankin Scale at 1 week as well). All four outcome scales were assessed at 3 months, as well as a repeat CT scan.

The primary endpoint of the Part 1 study was an evaluation at 24 hours of the percentage of patients with "Significant Early Improvement", defined as a 4 or more point improvement in NIH-SS from baseline to 24 hours, or complete recovery by 24 hours. In the course of designing the Part 2 study, a late-Part 1 study interim analysis of safety and efficacy was examined by the unblinded Data & Safety Monitoring Board (DSMB). Based on advice from the DSMB, the primary endpoint and analysis selected by the investigators for the Part 2 study was a Generalized Estimating Equations method to test a global statistic. This statistic incorporated the patient outcomes on all four clinical outcome scales, each of which was dichotomized to distinguish between a favorable outcome (complete or nearly-complete recovery) and less-favorable outcome. The dichotomization criteria for favorable outcome were: Barthel Index = 95-100; Modified Rankin = 0-1; Glasgow = 1; and NIH-SS = 0-1.

Because the clinical meaning of the global statistic was unclear, additional discussions between CBER and Genentech occurred. These discussions concluded that the individual outcome scales, each analyzed for percentage of patients with the designated favorable outcome and for effects upon the full ordinal scale outcome of the group were critical secondary endpoints to clarify the clinical meaningfulness of any treatment effects demonstrated by the global statistic.

In addition, important safety outcomes were the incidence of all-cause mortality and of intracranial hemorrhage. The protocol prospectively identified patients with aspirin usage prior to the stroke, and the two time strata (0-90 min, 91-180 min) for subgroup analyses.

An Intent-to-Treat analysis was the primary analysis, and a comprehensive data imputation plan was devised to allow inclusion of patients for whom there was any missing data.

Interim analyses of safety and efficacy were conducted periodically with results accessible only to the DSMB.

The protocol stated that the 3 month CT scan would be analyzed for infarct volume by centralized, blinded readers. However, these measurements were not completed in time for the PLA Supplement submission, and neither results nor primary data for this were supplied to CBER.

D. *The NINDS tPA Stroke Trial: Study Performance*

1. Enrollment

Patients were enrolled into the two studies between January 1991 and October 1994, with prospective assignment of patients enrolled on or after November 3, 1992 to the Part 2 study. There were 291 patients enrolled into the Part 1 study (144 Activase, 147 placebo) and 333

patients enrolled into the Part B study (168 Activase, 165 placebo), for a total of 624 patients in the combined studies (312 patients in each treatment arm).

2. Study population characteristics

Investigators at each treatment site maintained a screening log of all patients evaluated for ischemic stroke. Of the evaluated patients, approximately 3½% were enrolled into the studies. The largest number of excluded patients (52%) were on the basis of arrival in hospital too long after onset to meet the eligibility criterion of treatment within 3 hours. Another 17% were excluded due to symptoms too minor for inclusion or rapidly improving at the time of evaluation. Approximately 9% were excluded due to intracranial hemorrhage at the time of evaluation. Patient demographics and baseline status were generally balanced between the study treatment groups. The most notable exception was for aspirin usage prior to the stroke, where Activase treated patients had a greater frequency of usage with the 2 weeks prior to the stroke. Few patients (approximately 5%) had changes on the baseline CT scan typical for acute stroke, such as edema or mass effect. The degree to which this is related solely to the short time limit (within 3 hours) from stroke onset, or in part due to an indirect exclusion criterion effect (see Eligibility Criteria above) is unknown.

3. Treatment characteristics

In each study, as required by the protocol design, approximately half of the patients had study treatment initiated within 90 min of stroke onset, half within the period 91-180 min. Overall, 302 of the 624 total patients (48%) were treated within 90 minutes of stroke onset. Within these 302 patients, over 200 were treated within the 85-90 min period.

E. *The NINDS tPA Stroke Trial: Efficacy Endpoint Results*

The primary endpoint of the Part 1 study, "Significant Early Improvement", was the change from baseline to 24 hours on the NIH-SS. This was also assessed in the Part 2 study. The results indicated a trend toward a larger number of patients showing early improvement with Activase vs. placebo in both Part 1 and Part 2 studies (8.1% Part 1; 8.2% Part 2 more patients with early improvement in the Activase group), but did not reach statistical significance in either study. This endpoint is an indicator of early activity, not an important measure of efficacy.

The 90 day outcome, using the dichotomized outcome scales and analyzed as a single global statistic was selected as the Part 2 study primary endpoint. The 90 day outcomes, both global and univariate scales, dichotomized and full ordinal scales, and both Part 1 and Part 2 studies are presented in the following table.

90 Day Outcome Assessment								
	Part 1 Study							
Outcome	Dichotomized Outcome ("Excellent Recovery")					Native Scale		
N	147	144				147	144	
	Placebo n %	Activase n %	%Recovery Difference	Relative Recovery	p-value[1]	Placebo median	Activase median	p-value[2]
Global				1.44	0.005			
Barthel	57 (38.8)	78 (54.2)	15.4	1.40	0.010	75	95	0.016
Rankin	40 (27.2)	68 (47.2)	20.0	1.74	0.001	3	2	0.010
Glasgow	45 (30.6)	67 (46.5)	15.9	1.52	0.006	2	2	0.016
NIH-SS	31 (21.1)	54 (37.5)	16.4	1.78	0.003	7	3	0.006
	Part 2 Study							
Outcome	Dichotomized Outcome ("Excellent Recovery")					Native Scale		
N	165	168				165	168	
	Placebo n %	Activase n %	%Recovery Difference	Relative Recovery	p-value[1]	Placebo median	Activase median	p-value[2]
Global				1.34	0.018			
Barthel	62 (37.6)	84 (50)	12.4	1.33	0.024	65	92.5	0.064
Rankin	43 (26.1)	65 (38.7)	12.6	1.48	0.015	3	3	0.035
Glasgow	52 (31.5)	74 (44)	12.5	1.40	0.020	2	2	0.050
NIH-SS	33 (20)	52 (31)	11.0	1.55	0.024	7	4.5	0.033

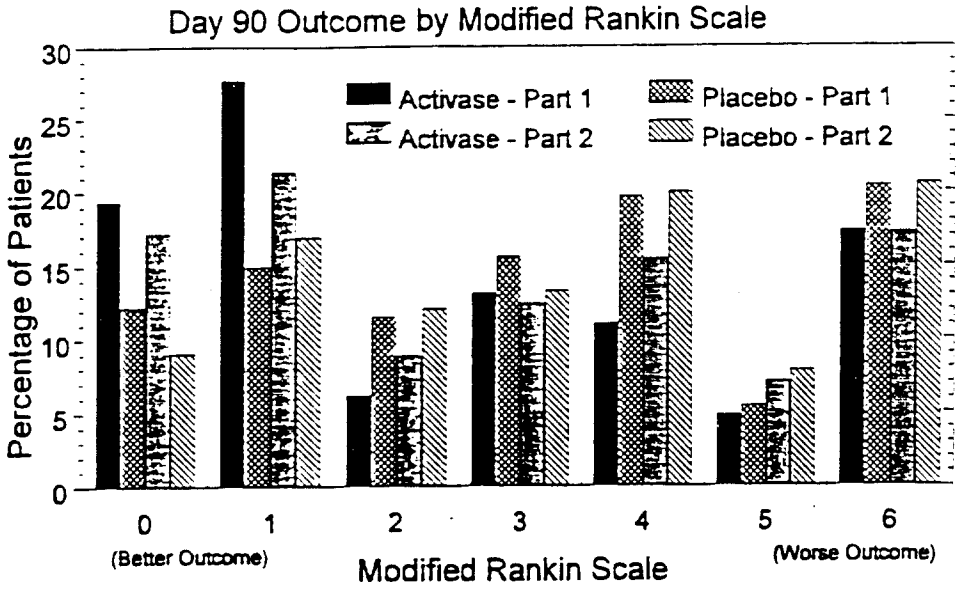
[1] p-value from GEE with log link; for univariate scales equivalent to CMH test

[2] p-value from Wilcoxon rank-sum test; all results in direction of better outcome with Activase, including instances when median scores are identical (Rankin and Glasgow)

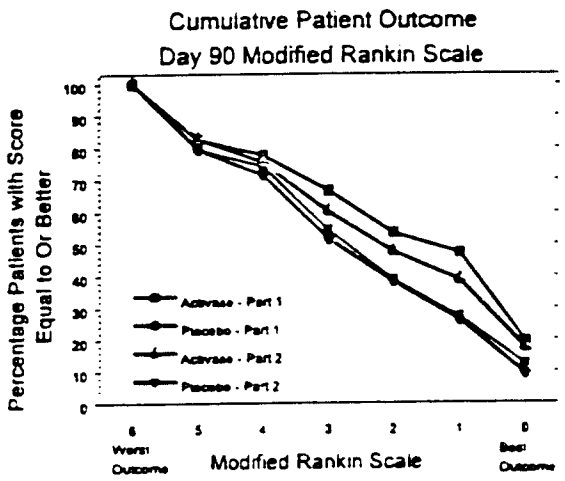
There were more patients in the Activase group who had favorable outcomes on the dichotomized scales, and these differences were statistically significant in both the Part 1 and the Part 2 studies. The treatment effects seen were consistent between the two studies.

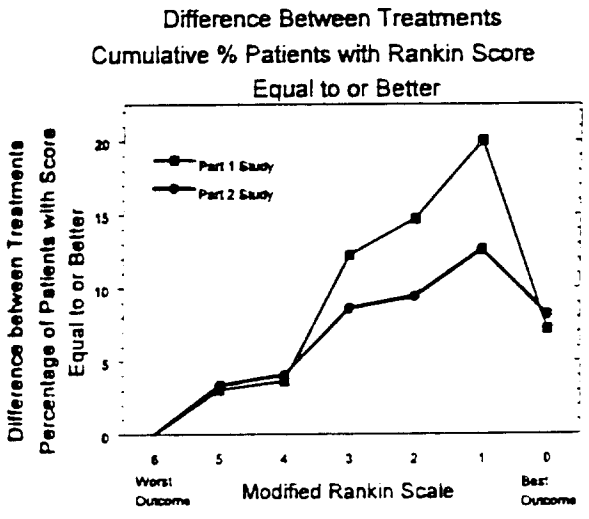
Comparison of the full ordinal scales showed significant differences, in the direction of improved outcome associated with Activase treatment. Intracranial hemorrhage is an expected risk with thrombolytic agents in acute ischemic stroke, leading to concern of increased frequency of the most unfavorable outcomes in Activase-treated patients. The absence of a bimodal shift in patient outcomes is more clearly seen in examining the actual frequencies of each score within each of the outcome scales, typified by the Modified Rankin Scale shown below.

Although there are relatively few categories in the Rankin Scale, the patients were broadly distributed across the available categories. The results were consistent between the two studies. There was a greater percentage of patients with the most favorable outcomes and fewer with each of the least favorable outcomes in the Activase-treated group as compared to the placebo group.



The cumulative percentages by Rankin score (below left) was also examined to better illustrate the treatment effects. This figure displays the percentage of patients with an outcome equal to or better than the plotted score. A higher curve describes a group with more patients distributed at better outcome scores, and the area between two curves provides a sense of the amount of additional good outcomes. Note that the horizontal scale is drawn with better outcome scores to the right.





The figure showing the differences between the cumulative percentage-score curves (above right) is the difference between the score-cumulative curves of each treatment group for each study. These curves indicate the Activase-associated additional percentage of patients with favorable

outcome calculated for dichotomization of the Rankin Scale at any specific score. When dichotomized at a score of 1 or better (as defined by the protocol), the Part 2 study showed an Activase-treatment effect of approximately 13% more of the patients with favorable outcome.

Because of the imbalance between the randomized groups in patients with a history of prior aspirin usage, and the importance of factors such as severity of stroke and age as predictors of outcome, the study results were re-analyzed with the addition of covariates. When baseline stroke severity and age (either as a categorized variable or as a continuous variable) as well as prior aspirin usage were used as covariates, there was only minor change in the results of the studies, either in the estimates of treatment effect or in the p-values. The manufacturer's covariate analysis also included weight, smoking, blood pressure or baseline PT in some analyses; there were no important changes in the estimate of treatment effect.

The analyses reported above were with patients grouped for analysis by actual treatment received, rather than as a true Intent-to-Treat. Note that the published account of the studies (NEJM 1995;333:1581-7) also utilizes this "As-Treated" analysis, rather than the Intent-to-Treat analysis as the report states. A sensitivity analysis of patients more in keeping with an intent-to-treat principle indicated that this difference did not have any significant effect on the conclusions that may be drawn from these studies.

F. *The NINDS tPA Stroke Trial: Safety Results*

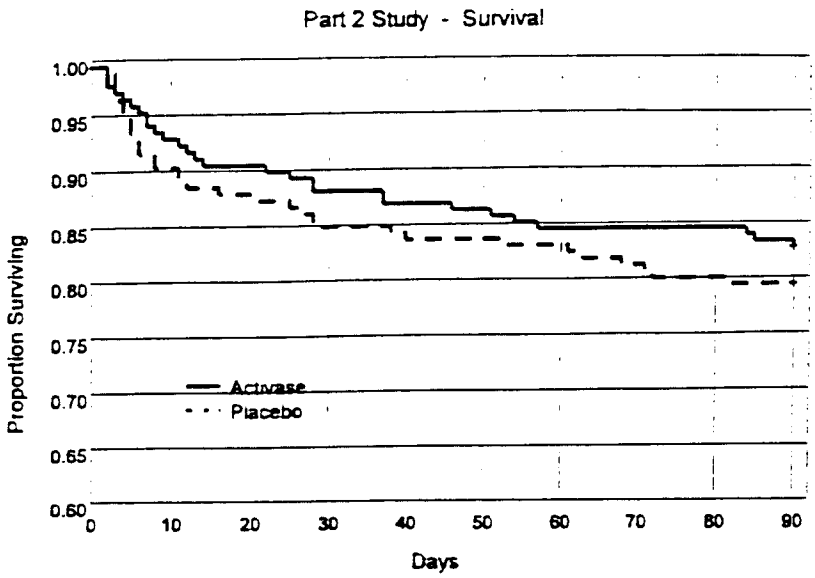
1. Mortality

Mortality rates were examined in the two studies. There was a trend to lower mortality at 90 days in the Activase group that was seen in both studies, but did not reach statistical significance.

	Mortality Rates									
Time point	Part 1 Study					Part 2 Study				
	Placebo (n=147)		Activase (n=144)		p-value	Placebo (n=165)		Activase (n=168)		p-value
	N	%	N	%		N	%	N	%	
90 days	30	20.4	25	17.4	0.55	34	20.6	29	17.3	0.48
All avail. f/u	47	32.0	34	23.6	0.12	43	26.1	44	26.2	1.0

p-values by Fisher's Exact test
All available f/u is of variable duration; up to 18 months for some patients

Within the 90 day time frame the Kaplan-Meier curves also illustrated the trend towards increased survival associated with Activase treatment, without any excess early mortality that might have been associated with the occurrences of ICH. The differences in the survival curves did not reach statistical significance (Part 1 study p = 0.505; Part 2 Study p = 0.424; Combined studies p = 0.296).



2. Intracranial Hemorrhage

Intracranial hemorrhage (ICH) was determined by central, blinded reading of the CT scans, both those obtained for evaluation of patients with clinical changes as well as the scans obtained according to the planned schedule. ICH events were divided into two categories based upon the observation or absence of an acute clinical worsening attributable to the ICH. These were termed Symptomatic and Asymptomatic ICH. These terms apply solely the acutely observed effects, and do not imply the absence of a long-term adverse clinical consequence associated with the "Asymptomatic" ICH events.

Occurrence of ICH was significantly greater in the Activase group than placebo, as shown in the following table. This was consistent between both studies.

Intracranial Hemorrhage

	Part 1 Study			Part 2 Study			Combined Studies		
	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value
N enrolled	147	144		165	168		312	312	
All ICH	9 (6.1)	19(13.2)	0.04	11(6.7)	29(17.3)	0.003	20 (6.4)	48 (15.4)	<0.001
Symptomatic ICH	2 (1.4)	11 (7.6)	0.01	2 (1.2)	14 (8.3)	0.003	4 (1.3)	25 (8.0)	<0.001
Asymptomatic	7 (4.8)	8 (5.6)	0.80	9 (5.4)	15 (8.9)	0.29	16 (5.1)	23 (7.4)	0.32
Any ICH Within 36 hours of Treatment	3 (2.0)	13 (9.0)	0.009	8 (4.8)	21 (12.5)	0.01	11 (3.5)	34 (10.9)	<0.001
Symptomatic ICH	0	8 (5.6)	0.003	2 (1.2)	12 (7.1)	0.011	2 (0.6)	20 (6.4)	<0.001
Asymptomatic ICH	3 (2.0)	5 (3.5)	0.46	6 (3.6)	9 (5.4)	0.45	9 (2.9)	14 (4.5)	0.29

NOTE The table does not include 3 ICH events occurring prior to treatment and retrospectively noted on the baseline CT scan during the central blinded review process.

p-values from Chi-Square test

The time course of occurrence of ICH was not uniform over time. Symptomatic hemorrhages occurred with a decreasing frequency over time in the Activase arm. Asymptomatic hemorrhages were largely ascertained at the time of the 24 hour CT scan. A small additional number were ascertained at the succeeding scheduled CT scan obtained sometime between days 7 to 10. There was a change in the differential incidence of hemorrhage between the two groups at approximately 36 hours after the stroke onset. The Activase group had markedly more hemorrhages than the placebo group before 36 hours (20 symptomatic, 14 asymptomatic in Activase patients compared to 2 symptomatic, 9 asymptomatic in placebo patients). After 36 hours the incidences were similar (5 symptomatic, 9 asymptomatic in Activase-treated, 2 symptomatic, 7 asymptomatic in placebo-treated patients). Thus, the increase in hemorrhages related to Activase treatment occurred largely within 36 hours of treatment.

3. Systemic Hemorrhage

Systemic bleeding (all non-ICH bleeding) events were also significantly more frequent in the Activase group. However, serious adverse events of hemorrhage, while increased in frequency, did not reach statistical significance.

Systemic Bleeding

	Part 1 Study			Part 2 Study			Combined Studies		
	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value
Any Bleeding	33 (22.4)	71 (49.3)	<0.001	71 (43.0)	97 (57.7)	0.007	104 (33.3)	168 (53.8)	<0.001
Serious Bleeding	1 (0.7)	4 (2.8)	0.169	4 (2.4)	3 (1.8)	0.685	5 (1.6)	7 (2.2)	0.560

p-values calculated with Chi-square test

The numbers of patients receiving transfusions during the study was also examined and were increased in frequency in the Activase patients.

Patients Receiving Transfusions During Studies

	Part 1 Study			Part 2 Study			Combined Studies		
	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value	placebo n (%)	Activase n (%)	p-value
Any type transfusn.	5 (3.4)	13 (9.0)	0.047	8 (4.8)	20 (11.9)	0.021	13 (4.2)	33 (10.6)	0.002
RBC transfusions	5 (3.4)	7 (6.9)	0.371	7 (4.2)	13 (7.8)	0.334	12 (3.8)	20 (6.4)	0.187
>2 U RBC	2 (1.4)	4 (2.8)		3 (1.8)	4 (2.4)		5 (1.6)	8 (2.6)	

p-values using Mantel-Haenszel Chi-Square

There were significantly more patients in the Activase group than placebo that required transfusions with the various kinds of transfusion products (including red blood cells, plasma,

cryoprecipitate, and platelets). However, only a relatively few patients required extensive transfusions. Furthermore, many of the transfusions utilizing cryoprecipitate or platelets were related to occurrence of a symptomatic ICH, not to a severe systemic bleeding adverse event. There was a higher number of patients receiving red cell transfusions in the Activase treated group than the placebo group, however this did not reach statistical significance.

4. Other Adverse Events

Genentech supplied a datafile of all adverse events reported by the investigators. The classification system used for organizing this information was neither COSTART nor another widely utilized system, so that the summary incidence rates of the event-type categories are not meaningful to compare either between treatment arms or to medically expected rates of specific types of events. The specific descriptions of the events were reviewed and did not indicate an obvious incidence of unexpected types of events in this clinical setting.

The risks of thrombolytic agents in general are understood based upon the extensive use of these agents in clinical practice, particularly for the treatment of acute myocardial infarction (MI). This patients with acute ischemic stroke are similar in prior general medical characteristics. Additionally, the dosage of Activase indicated for MI is larger than that studied in acute stroke (see pg. 3). General adverse events can be expected to be similar in the acute ischemic stroke setting to the prior experience with Activase in acute MI patients.

G. *The NINDS tPA Stroke Trial: Exploratory Analyses*

There was no significant difference in outcomes between the patients in the two time strata (0-90min and 91-180min). When patients were further subdivided by additional time-to-treatment distinctions, there was no time-related trend in treatment effect. Within the 3 hour limit for time from onset to treatment of these studies, there was no apparent time-to-treatment related difference in efficacy.

The Activase-treated patients who had aspirin use within 2 weeks prior to the stroke had a higher rate of ICH than Activase-treated patients without aspirin use, but this difference did not reach significance. In spite of this increase in ICH amongst the prior-aspirin-use patients, Activase treatment was still associated with improved outcome.

Subset analyses were also conducted based on the factors of patient baseline stroke severity (as indicated by the baseline NIH-SS), patient age, and weight. These *post hoc* selected factors were chosen based upon general knowledge from the medical literature of factors that might be predictors of differential risks.

As expected from the medical literature, both baseline stroke severity and patient age were important predictors of outcome. Patients have poorer outcome in both treatment groups with increasing severity or increasing age. Both increasing baseline stroke severity and increasing age were also associated with a trend towards decreased treatment effect on the outcome scales and increased ICH in the Activase-treated patients. The trends towards lessened favorable outcome and increased ICH become particularly prominent in the approximately 20% of patients with the

most severe strokes (NIH-SS > 22) or most advanced age (age > 77 yr). Analyses based on patient weight indicated that weight was not an important treatment effect modifier.

H. *ECASS: The European Cooperative Acute Stroke Study*

The ECASS protocol was conducted in Europe by Boehringer-Ingelheim, manufacturer a different tissue plasminogen activator (alteplase), Actilyse. It is an important study as it provides data on a large group of patients in a similar clinical setting treated with a similar regimen. ECASS did not show improvement of patient outcome with alteplase treatment. However, there are important differences in the ECASS study compared to the NINDS study so that conclusions must be carefully considered.

1. Design

The objective of this randomized, double-bind, placebo-controlled study was to evaluate the efficacy and safety of alteplase in acute ischemic stroke patients who are treated within 6 hours from the onset of symptoms. Eligibility criteria were generally similar to that of the NINDS Stroke Study. Notable differences were in time from onset of stroke to treatment (up to 6 hours in ECASS vs. 3 in the NINDS study), and marked CT scan abnormalities typical of acute stroke were explicit exclusion criteria. Study treatment was either IV placebo or IV Actilyse at 1.1mg/kg, to a maximum of 100mg, given as 10% bolus, 90% in a 1 hour infusion. Subcutaneous heparin was permitted upon hospital admission, IV heparin was prohibited until 24 hours after treatment. Antiplatelet agents were recommended, and to begin at 24 hours after treatment.

The 3 month Barthel Index and the 3 month Rankin Scale were the dual primary efficacy endpoints. As it was anticipated that some patients enrolled would subsequently be deemed eligibility violations, the analytic plan called for a "per protocol" secondary analysis of non-protocol-violation patients.

2. Study Subjects

There were 620 subjects enrolled and randomized (307 placebo, 313 Actilyse), with a total of 109 patients (43 placebo, 66 Actilyse) retrospectively excluded from the evaluable ("per protocol") population. Almost half of the exclusions (52) were for major early infarct signs identified on the CT scan at a later, blinded reading of the scans, with an additional 12 patients excluded for not performed or inadequate baseline CT scans.

Baseline reported characteristics of the ECASS patients are largely similar to those of the NINDS study patients. The mean time from onset to treatment was approximately 4.4 hours; only 15% of the patients were treated within 3 hours of onset.

3. Efficacy Endpoint Results

The efficacy results of ECASS are shown in the following table. Also included for comparison is the dichotomized Rankin Scale, as calculated for the NINDS study.

ECASS Efficacy Results						
90 day outcomes	ITT Analysis			PP Analysis		
	Placebo	Actilyse	p-value	Placebo	Actilyse	p-value
N	307	313		264	247	
Barthel Index, median - mean	75 61.7	85 62.9	0.99	80 63.2	90 66.4	0.18
Rankin Scale, median : mean	3 3.1	3 2.9	0.41	3	2	0.035
Rankin Scale, score 0-1 (%)	29	35				

Notes: Barthel includes deaths, as lowest score
Rankin include deaths as lowest score

ECASS did not demonstrate efficacy of the regimen of Actilyse utilized in the study.

4. Safety Results

Both mortality and ICH were reported as a specific outcomes of the study. Mortality occurred at a higher rate in the Actilyse-treated group than in the placebo group.

ECASS Mortality Results								
Mortality Outcomes	ITT Analysis			PP Analysis			Excluded Patients	
	Placebo	Actilyse	p-value	Placebo	Actilyse	p-value	Placebo	Actilyse
N	307	313		264	247		43	66
Deaths by day 90	48 (15.6%)	69 (22%)	0.04	39 (14.8%)	48 (19.4%)	0.20	9 (20.9%)	21 (31.8%)
Time to treatment < 3hrs	21% of 40	26% of 52	0.62	21% of 29	26% of 39	0.78		
Time to treatment > 3hrs	15% of 267	22% of 261	0.06	14% of 235	18% of 208	0.24		
90d mortality; only patients with early major infarct signs							6 / 21 (28.6%)	15 / 31 (48.4%)

p-values with Fisher's's Exact test
mortality of patients with early major infarct signs inferred from supplied results, some uncertainty exists in this result

As this was also true in the small subset of patients who were treated within 3 hours of stroke onset, the difference in mortality between the ECASS and NINDS Stroke Study cannot be attributed to just the difference in time to treatment between the two studies. Mortality was particularly high in the subset of patients who had early major infarct signs on the baseline CT scan.

ICH in the ECASS study occurred at higher rates in the Actilyse group, as well as at higher rates than was seen in the NINDS Stroke Trial.

ECASS Intracranial Hemorrhage Events

	ITT Analysis			PP Analysis			Excluded Patients	
	Placebo (n=302)	Actilyse (n=305)	p-value	Placebo (n=264)	Actilyse (n=245)	p-value	Placebo (n=38)	Actilyse (n=60)
Total ICH	113 (36.8%)	134 (42.8%)	0.10	97 (36.7%)	107 (43.7%)	0.148	16 (42.1%)	27 (45%)
Hemorrhagic Infarction	93 (30.8%)	72 (23.6%)		79 (29.9%)	59 (23.9%)		14 (36.8%)	13 (21.7%)
Parenchymal Hematoma	20 (6.6%)	62 (20.3%)		18 (6.8%)	48 (19.4%)		2 (5.3%)	14 (23.3%)

p-values using Fisher's Exact test
n's exclude patients with missing CT scans: ITT - 5 placebo, 8 Actilyse; PP - 0 placebo, 2 Actilyse;

In ECASS there was an Actilyse associated increase in parenchymal hematomas. This is consistent with the effect seen in the NINDS studies, where symptomatic hemorrhage was significantly increased. While the two studies methods of characterizing ICH are not equivalent, there will be much overlap between ECASS' parenchymal hematoma and NINDS' symptomatic ICH.

5. Conclusions

ECASS results showed an unfavorable risk-benefit comparison of the thrombolytic regimen. Outcome scales were not significantly different between the two treatment groups, but there was a higher mortality rate with Actilyse. This was likely related to the higher rate of ICH with Actilyse, particularly parenchymal hematomas. When 18% of the patients were excluded, there were some trends to efficacy; however the excess ICH and mortality still remained. There were no statistical differences between the patients treated within 3 hours of stroke onset and those within the 3-6 hour period.

There were considerable differences in ECASS design from the NINDS Stroke Trial. These include that ECASS used a dose of tPA approximately 22% higher than the NINDS study. The hypothesis that this might indicate a narrow therapeutic index for tPA remains unproven.

The "per protocol" excluded patients are of particular interest. Almost half of these patients had marked changes on the screening CT scans. Although these patients did not have ICH rates markedly different from the other patients, a larger fraction trended towards parenchymal hematomas, and their mortality rates were somewhat higher. Mortality at day 90, while higher in patients with early major CT infarct signs overall, was doubled with Actilyse treatment as compared with placebo. Thus, these patients may be a definable subset that are at particular risk for mortality related to ICH. The ECASS patients present the primary source of information regarding this subset of patients, as these patients were not enrolled in the NINDS Stroke Study.

I. *The NINDS Pilot Study*

Development of this therapy included a phase 2 pilot study to examine range of doses and a different dosage regimen. The information submitted by Genentech is largely limited to that of the published reports.

Design: Conducted in sequential dose tiers at 3 centers, this was an open label study except for the small last cohort which was placebo controlled and blinded. Safety, assessed as bleeding events, both intracranial and systemic serious bleeding, was the primary objective. Clinical status at 3 months and CT scans were also evaluated to provide a potential evidence of therapeutic activity. Angiograms were not performed as part of this study.

Patient population: Initially limited to patients with acute ischemic stroke presenting soon after onset of the stroke such that treatment could be initiated within 90 minutes of stroke onset. Modifications to the original protocol subsequently included a group of patients in the 90 to 180 minute period from onset to treatment, to assess safety in these patients. The eligibility criteria were essentially the same as for the pivotal trial conducted by the NINDS investigator group. Small modifications occurred in eligibility criteria during the trial, such as in laboratory results and blood pressure limits, that eventually led to those adopted for the pivotal trial.

Dose Tiers, Regimens and Patient Enrollment

Tier	Dose amount	Reported as (mg/kg)	Regimen	Total Patients
I:	0.35 mg/mg (max 25mg)	0.35	no bolus, 1 hr infusion;	6
II:	0.6 mg/kg (max. 40mg)	0.60	no bolus, 1 hr infusion;	20
III:	0.85 mg/kg (max 60mg)	0.85	no bolus, 1 hr infusion;	10
IV:	32mg/m2 (max 90mg)	0.85	10% bolus, 1hr infusion	26
V:	37.6 mg/m2 (max 90mg)	0.95	10% bolus, 1 hr infusion	3
IVExt	32mg/m2 (max 90mg) + 5.5mg/m2	0.95	no bolus, 1 hr infusion + 30 min infusion for following part	28
VI	45mg/m2 (max 100mg)	1.08	10% bolus, 45% in 30 min infusion then 45% in 1 hr infusion	1
Controlled	same dose as IVExt.	0.85	placebo controlled, blinded; IVExt regimen	14 + 13

Notes: 1) Results were reported as approximate average mg/kg received for the patients actually enrolled in groups IV to VI. so that all groups were regarded as dosed on mg/kg basis.

2) The protocol designates the controlled patient group to receive the Tier IVExt regimen, the published account describes the Tier IV regimen as utilized

Safety results in the open label portion indicated that 5 ICH occurred, 1 in Tier IV, 3 in Tier IVExt, 1 in Tier V, with a scattering of hemorrhagic transformation without hematoma or other asymptomatic hemorrhage in dose tiers I to IVExt. There were 18 deaths within the 90 day period, distributed through dose tiers I to IVExt.

In the controlled and blinded portion, there was no ICH in the Activase treated patients. There were 3 deaths in the placebo group and 1 in the Activase group by 3 months. The results were deemed encouraging and worthy of further evaluation in a controlled trial. This led to the initiation of The NINDS tPA Stroke Trial.

J. *The TTATTS Study (Thrombolytic Therapy of Acute Thrombotic / Thromboembolic Stroke Study)*

This was a multicenter, dose escalation, angiographic study of Activase in acute stroke.

Design

This study was an open label, non-randomized dose escalation study of intravenous Activase in acute ischemic stroke patients. In addition to an eligibility screening process similar to that used in the NINDS pilot and pivotal trials, these patients were required to angiographically demonstrate obstruction to flow (TIMI Grade 0) in an arterial vessel appropriate for the clinical signs. Patients with a complete occlusion were treated with Activase at dose levels of 0.8 and 1.0 mg/kg, given as 10% bolus, the remainder by a 1 hr infusion. Dose levels of 1.2 and 1.4 mg/kg had been planned, but were not initiated due to early termination of the study. Eligibility was restricted to patients who could begin treatment within 6 hours of stroke onset. In addition to clinical assessments of outcome, a repeat angiogram was performed at 2 hrs after initiation of the Activase. Patient followup was only through 10 days.

Results

There were 24 patients enrolled at 0.8mg/kg, and 14 patients at 1.0mg/kg. There were 10 ICH in the 24 patients in the 0.8mg/kg group (4 symptomatic, 6 asymptomatic) , and 7 ICH in the 14 patients in the 1.0mg/kg group (4 symptomatic, 3 asymptomatic). The occurrence of 4 of 14 patients with symptomatic ICH in the 1.0mg/kg group let to early termination of the study for safety reasons. Of the 8 patients with symptomatic ICH, 4 died (2 each in each dose level).

In the 0.8 mg/kg dose group, 2 of 18 patients had a complete response of flow restoration, 4 of 18 had a partial response, and 12 had no response. In the 1.0 mg/kg group, 1 of 13 had complete response, 2 of 13 had a partial response, and 10 had no response. Thus, recanalization rates were low in this study.

The review of the adverse events in these few patients and their characteristics indicated that more of the patients with medical histories of CHF or atrial fibrillation experience serious adverse events than without these characteristics. Patients with more severe strokes had a tendency toward a greater incidence of ICH. There was also a tendency of patients with ICH having had higher systolic blood pressures. None of these associations were statistically significant in this small group of patients.

Conclusion

This study utilized a protocol that involved selection of patients with angiographically proven occlusions and a repeat angiogram to assess recanalization. The patient population also differed from the NINDS studies in allowing up to 6 hours from onset to initiation of treatment. The results of this study indicated higher rates of ICH than was observed in either of the NINDS

studies. The rates of ICH were not dissimilar between the two dose levels, but this study does not have sufficient power to demonstrate even moderate differences. Whether the angiogram, the time from onset to treatment, or other factors influenced the ICH rate cannot be determined.

K. *Clinical Information Summary*

- The NINDS Stroke Trial consisted of two randomized, double-blind, placebo-controlled, multicenter studies designed to assess the efficacy and safety of 0.9mg/kg IV Activase in acute ischemic stroke patients who could have treatment initiated within 3 hours of stroke onset.

- The primary efficacy endpoint was a global statistic comprised of the dichotomized forms of four stroke outcome scales, assessed at 90 days after the stroke onset. Supportive analyses included individual consideration of each of the four univariate scales, in both the dichotomized and full ordinal forms.

- The two trials were conducted immediately consecutively. All procedures, investigators and treatment sites were identical in the two studies. Each trial was of a size large enough to be well powered to detect treatment effect.

- The Primary Efficacy Endpoint of the Part 2 Study was selected by the unblinded Data and Safety Monitoring Committee with complete knowledge of a late trial interim analysis of the Part 1 Study. Thus the Part 2 Study is the hypothesis testing study, the Part 1 Study providing confirmatory evidence.

- The 90 day outcome assessments, in the tests of the global statistic, the univariate scales in dichotomized form, and the univariate scales in full ordinal form all demonstrated significantly better outcomes in the Activase group. This was true for the Part 2 Study as well as the Part 1 Study.

- The two treatment groups exhibited modest imbalances in some characteristics that may be significant predictors of outcome. Covariate-adjusted analyses that accounted for the baseline imbalances did not qualitatively alter the comparison between treatment groups.

- There was a trend to lower mortality with Activase that did not reach statistical significance in either study alone, nor in the combined dataset.

- Intracranial hemorrhage (ICH) was significantly higher with Activase treatment vs placebo. This was effect was most pronounced within 36 hours of treatment. Although ICH is associated with poor outcome, the Activase group did have significantly better 90 day outcomes in spite of the increase in ICH.

- Severity of the acute stroke and patient age are important predictors of outcome, independent of treatment. Patients with more severe strokes or patients who are older

may have decreased risk-to-benefit comparisons associated with treatment with Activase. These factors become most important in the approximately 20% of the patients with most severe stroke patients (baseline NIH-SS > 22) or of advanced age (age > 77 yo), but no specific cutoff can be determined at which risk-benefit becomes definitively unfavorable.

- Multiple exploratory analyses to identify patient subgroups that might have unfavorable risk-to-benefit comparisons were examined. Several factors were post hoc identified which give rise to concerns of lessened favorableness of Activase treatment. These include patients with diabetes, history of CHF, Hispanic patients, and baseline fibrinogen of < 200. While no firm conclusions regarding these factors can be drawn, they are of potentially significant enough importance to warrant further investigations.

- The European Cooperative Acute Stroke Study (ECASS) was a large, placebo controlled, European study with a dose regimen of Actilyse -tPA that was 22% higher than in the NINDS Stroke Trial. Most patients in ECASS were treated more than 3 hours after onset of stroke.

  ECASS did not demonstrate a beneficial treatment effect. There was no significant difference in outcome between the ECASS patients treated prior to 3 hours after onset and those treated more than 3 hours after stroke onset. Mortality was significantly higher in Actilyse patients, as was ICH. Patients with early major infarct signs on the baseline CT scan appeared to have a particularly increased rate of parenchymal hematoma and mortality associated with Actilyse treatment.

- Adverse events other than ICH seen in these studies were not unusual for this patient population. The adverse events were not different from the known risks of treatment with Activase based on the experience in the setting of acute myocardial infarction.

VI. Advisory Committee Meeting and Recommendation

Data regarding the safety and efficacy of Alteplase in the treatment of stroke were discussed at the Peripheral and Central Nervous System Drugs Advisory Committee meeting on June 6, 1996. The committee voted 10 to 0 to recommend approval. The committee indicated that recommended treatment should be limited to within three hours after stroke onset, and after exclusion of an intracranial hemorrhage by a computerized tomography scan. They also concluded that there was an increased risk of intracranial hemorrhage associated with treatment in patients with increasing severity of the stroke, and for patients of advanced age. They recommended that treatment should be limited to facilities that can provide appropriate evaluation and management of intracranial hemorrhage.

VII. Phase 4 Commitments

As a condition of approval, Genentech has committed to performing the following phase 4 actions:

1. To continue the current ongoing investigation to evaluate the safety and efficacy of Activase treatment in patients presenting for treatment more than 3 hours after stroke onset.

2. To conduct a post-marketing, uncontrolled, clinical study of patients treated within 3 hours of stroke onset. This study will utilize a prospective design and collect demographic and baseline status information as well as safety and clinical effect outcomes. This protocol will be submitted to CBER for review and comment in advance of study initiation. This study will be analyzed to examine for patient characteristics that may describe patient subsets of increased risk with Activase treatment. Any decision to terminate this study will only be upon the concurrence of CBER.

3. To provide information from the European Cooperative Acute Ischemic Stroke Study (ECASS), specifically the dataset in electronic form, associated documentation, and safety analyses of these data as requested by CBER.

VIII. Approved Package Insert

A copy of the approved package insert is attached.

Signatures of the Licensing Committee

Marc Walton, M.D., Ph.D., Chair

Robert Brown, M.D., Ph.D.

Ghanshyam Gupta, Ph.D.

Christopher Joneckis, Ph.D.

Rocio Llave